REMARKS

Claims 5-16 are pending with claims 11-16 added by this paper. Support for claims11-16 can be found in the specification at page 2, lines 18-21.

Specification Objections

Attached hereto is an Abstract of the Disclosure on a separate sheet.

Reference to the parent application was incorporated in the specification by the amendment made in the transmittal letter submitted with the original filing on December 10, 1999. Reference to the parent application has been updated by the amendment above.

The Action objects to Applicants failure to file a certified copy of the foreign application in the present divisional application. The Office acknowledged receipt of the priority document in the parent application in the paper mailed November 29, 1999. Where the benefit of a foreign filing date is claimed in a divisional application and a certified copy of the foreign application was filed in the parent application, it is not necessary to file an additional certified copy in the divisional application. See M.P.E.P. §2114(b) at page 200-86.

In view of the above remarks, Applicants respectfully submit that the objections have been responded to and should be withdrawn.

Claim Rejection Under 35 USC §103

Claims 5-10 stand rejected as allegedly being unpatentable over U.S. Patent No. 4,357,324 (Montgomery). The Action admits that, "Montgomery does not specifically state that the purity of the compound was greater than 99.5%." However, the Action alleges that one of skill in the art would have reasonable expectation of success in the attainment of a purity of at least 99.5%, by post HPLC and ion-exchange purification steps. In addition, the Action alleges that one could easily repeat this step to obtain even higher purity if desired. Applicants traverse the rejection and maintain there is no evidence to support the allegations upon which the rejection is based. These allegations are based on speculation. In the absence of any supporting evidence, a showing of prima-facie obviousness has not been made and the rejection under 35

USC §103 should be withdrawn.

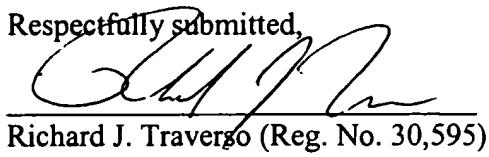
While conventional HPLC methods and ion-exchange purification steps are known to be effective purification techniques for many compounds, there is no evidence that these techniques will achieve the purity levels (less than 0.5 % impurities) of the fludara compounds of the compositions claimed herein or compounds similar to the fludara compounds. There is also no evidence that repetition of these conventional purification techniques will achieve these levels of purity for fludara compounds or compounds similar to fludara compounds. Applicants have achieved these levels of purity through a novel process described in U.S. Patent 6,046,322. These novel techniques do not provide any evidence or suggestion to support the assumption the techniques disclosed by Montgomery '324 are adequate to achieve the compositions claimed.

Commercially available fludara is less than 98% pure. Prior to this invention, Applicants have employed conventional ion exchange chromatography techniques, as used by Montgomery '324, to improve the purity level of fludara above 98%. For example, Applicants use of ion exchange chromatography techniques is disclosed in commonly assigned German Patent DE 19543052A1, attached hereto. Applicants have found that conventional ion exchange chromatography techniques yield only a 99.19% pure fludara composition. These results are reported in the attached table on page 6, column 2 under the heading "impurity content [%]." Based on theses results, Applicants submit the ion exchange purification process relevant to Montgomery '324 cannot be expected to provide a fludara product that is more than 99.19% pure. Consequently, the disclosure by Montgomery '324 cannot teach or suggest fludara products of at least 99.5% purity, as claimed herein, and the rejection under 35 USC §103 is untenable.

In contrast to compositions purified by ion exchange purification processes, Batches 1-3, disclosed in the last three columns of the attached table, were created by the novel and unobvious methods of the present invention disclosed in U.S. Patent 6,046,322 . These compositions have a purity of more than 99.37% fludara, and in one instance purity of 99.57% fludara (see Batch 2). Applicants respectfully submit such compositions are novel and unobvious.

In view of the above remarks, Applicants submit that the objections and the rejection under 35 USC §103 should be withdrawn. If there are any remaining issues which can be expedited by a teleconference, the Examiner is courteously invited to telephone counsel at the telephone number indicated below.

Respectfully submitted,



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Attorney Docket No.: SCH 1615 D1

Date: **July 9, 2002**

VERSION SHOWING THE CHAGES MADE

IN THE SPECIFICATION:

Please amend the first paragraph on page 1 to read as follows:

This is a division of application Serial No. 09/208,587, filed December 10, 1998, now U.S. Patent No. 6,046,322. This application claims the benefit of the filing date of U.S. provisional application Serial No. 60/069,778, filed December 16, 1997.

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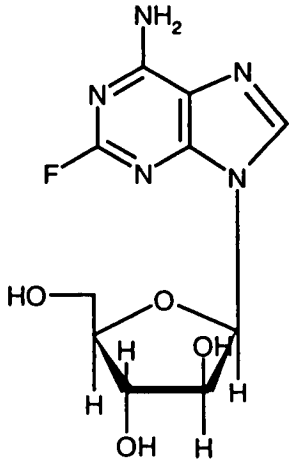
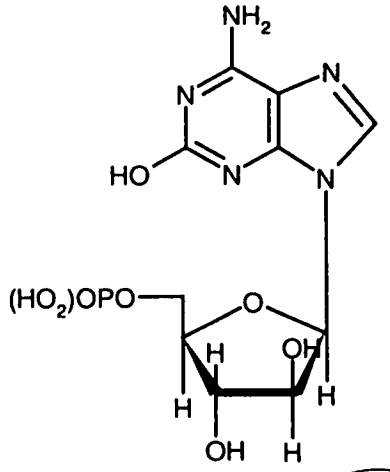
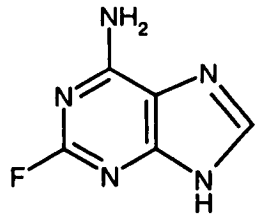
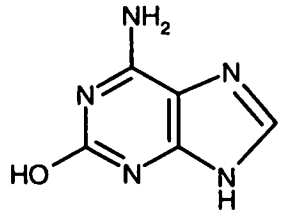
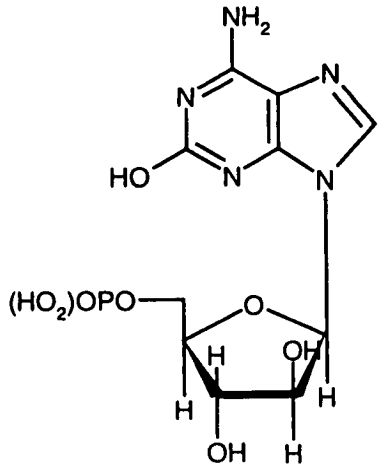
Abstract

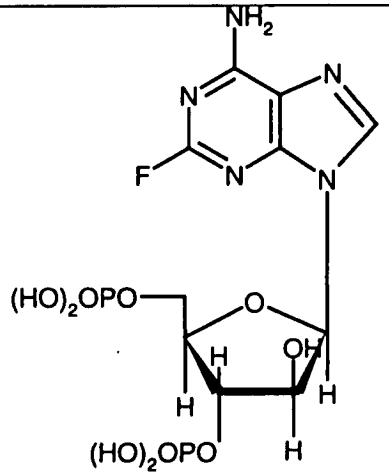
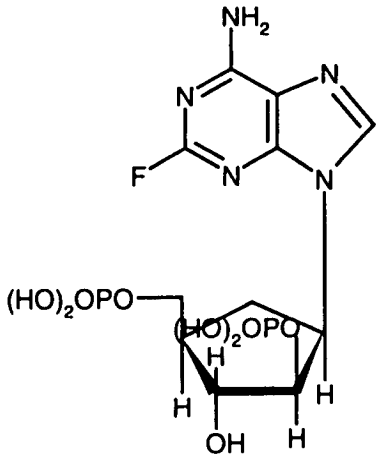
The present invention generally relates to a fludarabine-phosphate with a purity of at least 99.5%.

Com-pound No.	Structure	Chemical name according to IUPAC	Impurity content [%]				
			<98% pure Fludara	Ion exchange purification	Batch 1*	Batch 2*	Batch 3*
1		2- Fluoro-9-(ß-D-arabinofuranosyl)-9H-purin-6-amin	0,14	0,01	0,02	0,01	0,01
2		6-Amino-9(5-O-phosphono-ß-D-arabinofuranosyl)-9H-purin-2-ol	1,38	0,38	0,11	0,09	0,12

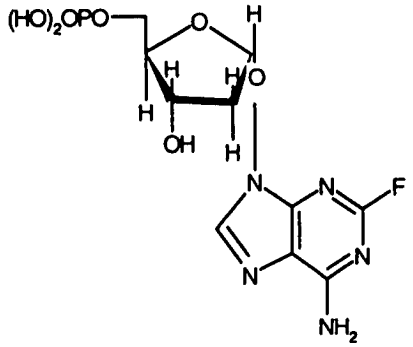
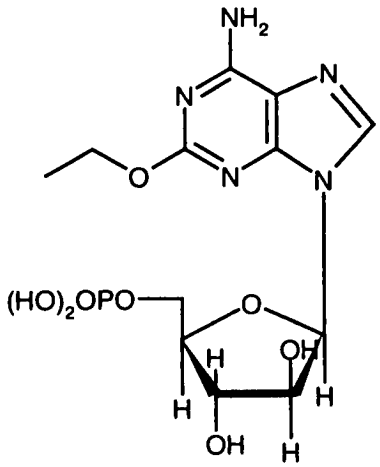
*inventive Fludara

Com-pound No.	Structure	Chemical name according to IUPAC	Impurity content [%]				
			<98% pure Fludara	Ion exchange purification	Batch 1*	Batch 2*	Batch 3*
3		2-Fluoro-9H-purin-6-amin	0,03	0,05	0,02	0,02	0,02
4		6-Amino-9H-purin-2-ol	0,25	0,02	<0,02	0,02	<0,02
5		2-Fluoro-9-(5-O-phosphono-ß-D-ribofuranosyl)-9H-purin-6-amin	0,02	0,02	0,04	0,03	0,05

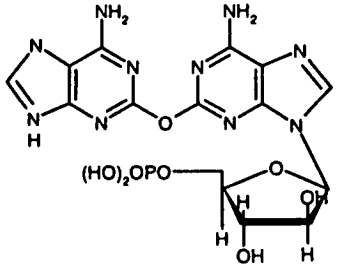
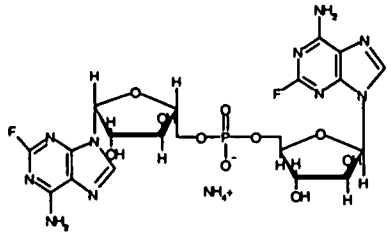
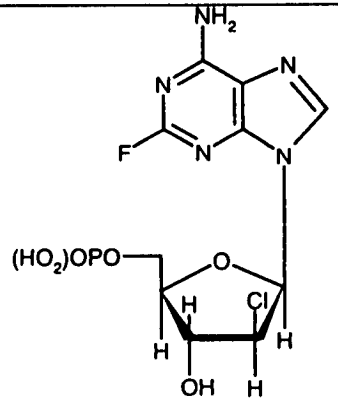
*inventive Fludara

Compound No.	Structure	Chemical name according to IUPAC	Impurity content [%]				
			<98% pure Fludara	Ion exchange purification	Batch 1*	Batch 2*	Batch 3*
6		9-(3,5-O-diphosphono-ß-D-arabinofuranosyl)-2-fluoro-9H-purin-6-amin	0,06	0,06	0,1	0,09	0,08
7		9-(2,5-O-diphosphono-ß-D-arabinofuranosyl)-2-fluoro-9H-purin-6-amin	0,03	0,02	0,1	0,09	0,08

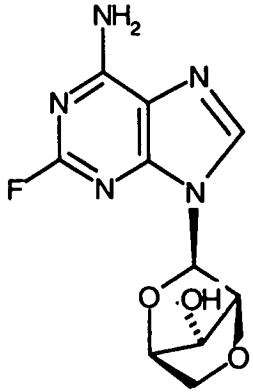
*inventive Fludara

Com-pound No.	Structure	Chemical name according to IUPAC	Impurity content [%]				
			<98% pure Fludara	Ion exchange purification	Batch 1*	Batch 2*	Batch 3*
8		2-Fluoro-9-(5-O-phosphono-ß-D-arabinofuranosyl)-9H-purin-6-amin	0,02	0,01	<0,02	<0,02	<0,02
9		2-Ethoxy-9-(5-O-phosphono-ß-D-arabinofuranosyl)-9H-purin-6-amin	0,26	0,02	0,06	0,01	0,01

*inventive Fludara

Com-pound No.	Structure	Chemical name according to IUPAC	Inmpurity content [%]				
			<98% pure Fludara	Ion exchange purification	Batch 1*	Batch 2*	Batch 3*
10		2-(6-amino-9H-purin-2-yl)-9-(5-O-phosphono-ß-D-arabinofuranosyl)-9H-purin-6-amin	0,05	0,14	0,02	0,02	0,02
11		O,O'-Bis[2-(6-amino-2-fluoro-9H-purin-9-yl)-5-deoxy-α–D-arabinofuranos-5-yl]-phosphate, Ammonium salt					
12		9-(2-Chlor-2-deoxy-5-phosphono-ß-D-arabinofuranosyl)-2-fluoro-9H-purin-6-amin	0,05	0,01	0,06	0,03	0,1

*inventive Fludara

Com-pound No.	Structure	Chemical name according to IUPAC	Inmpurity content [%]				
			<98% pure Fludara	Ion exchange purification	Batch 1*	Batch 2*	Batch 3*
13		9-(2,5-O-Anhydro-ß-D-arabinofuranosyl)2-fluor-9H-purin-6-amin	0,04	0,12	0,06	0,03	0,1
Complete Inpurities			2,33	0,81	<0,63	<0,43	<0,63

*inventive Fludara

Result:

- Commercial produced Fludara: max. 97,67% pure Fludara
- Ion exchange purification : max. 99,19% pure Fludara
  (using commercial produced Fludara)
- Fludara produced via the disclosed process, using the di-sodium salt >99,37% up to >99,57% pure Fludara

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